CLUB PHASE 1
FRENCH SAE REGISTER
2004-2009

ASCPT Dallas 2011

Serious adverse events in early drug development : results from a 6-year survey conducted in France by the Club Phase 1.

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BACKGROUND: **The Club Phase 1 (CPI) is a French, non-profitable association of clinical pharmacologists from Contract Research Organisations (CRO), pharmaceutical companies and academia (www.clubphase1.org).**

METHODS: **In an attempt to assess the safety risk for healthy subjects participating in phase 1 clinical trials conducted in France, CPI collected information on serious adverse events (SAEs) (as defined in the Good Clinical Practice i.e death, life-threatening, requires hospitalisation, disability, congenital anomaly and medically important event) through a survey using a questionnaire sent to all private CROs and academic Centres for Clinical Investigation. Collected information is recorded in an annual register.**

RESULTS: **This present study reports SAEs data collected from Phase I activities in France from 2004 to 2009. The questionnaire response rate was greater than 90%. During this 6-year period, 38227 healthy subjects were administered at least 1 dose of active compound or placebo (36158 male and female subjects aged 18-65 and 2069 elderly subjects aged above 65 years old). One hundred and fifty four (154; 0.4%) SAEs were recorded: 100 (65%) were considered not drug-related and 54 (35%) were possibly drug-related. The latter were then assessed based on their severity and/or medical importance, in order to identify those that were of concern. Sixteen (16; 0.04%) were considered as clinically worrying events, which included acute liver injury, rhabdomyolysis, cardiac arrhythmia, anaphylaxis, rash, convulsion and agranulocytosis. All subjects who reported possibly-related SAEs recovered. The incidence of SAEs reported by young/middle-aged and elderly subjects was 0.04% and 0.1%, respectively.**

CONCLUSION: **In summary, the occurrence of possibly-related and clinically worrying SAEs reported by healthy subjects was relatively low (0.04%) and was stable over the 6-year period studied. These results confirm that the risk for healthy volunteers participating in early drug development is minimal under controlled phase 1 safety conditions.**

Serious Adverse Events in Phase I - French Club Phase I Register 2004-2009

METHODS

Survey sent to CROs and CICs

Scope: Phase I studies in healthy subjects

Serious Adverse Event (GCP definition): Any untoward medical occurrence that at any dose:

- **Results in death**
- **Is life-threatening**
- **Requires inpatient hospitalization or prolongation of an existing hospitalization**
- **Results in a persistent or significant disability or incapacity**
- **Results in cancer**
- **Results in a congenital anomaly or birth defect**

Data : 6 years (2004-2009)

Serious Adverse Events in Phase I - French Club Phase I Register 2004-2009

POPULATION

Healthy subjects	All (100%)	Young		Elderly	
		Men	Women	Men	Women
2004	5458	79%	14%	3%	3%
2005	9928	73%	24%	1%	1%
2006	5927	61%	27%	7%	5%
2007	5782	71%	26%	1%	2%
2008	6331	71%	25%	1%	1%
2009	4801	71.5%	21%	2.5%	5%
Total	38227	71%	23%	3%	3%

Serious Adverse Events in Phase I - French Club Phase I Register 2004-2009

SAE INCIDENCE

SAE	Total number and incidence (%)		Related (number, %, incidence)			Unrelated (number, %, incidence)		
2004	**25**	**4‰**	10	40%	2‰	15	60%	3‰
2005	**35**	**3‰**	20	57%	2‰	15	43%	1.5‰
2006	**44**	**7‰**	10	23%	2‰	34	77%	5‰
2007	**15**	**4‰**	4	27%	0.7%	11	73%	2‰
2008	**25**	**4‰**	7	28%	1‰	18	72%	3‰
2009	**10**	**2‰**	3	30%	0.6‰	7	70%	1.5‰
Total	**154**	**4‰**	**54**	**35%**	**1.4‰**	**100**	**65%**	**2.6‰**

About a third of SAEs are drug related
Unrelated SAEs : Out of 100 drug unrelated SAE, 26 SAEs are due to Screening default
Causes of unrelated SAE : Intercurrent diseases (Cancer, Infection, Surgery, Traumatism…)

Serious Adverse Events in Phase I - French Club Phase I Register 2004-2009

RELATED AND WORRYING SAE

Population		Total SAE	Incidence SAE	Related and worrying SAE	
Young	**36158**	**129**	**3.5 0/00**	**14**	**0.4 0/00**
Male	27193			13	0.5 0/00
Female	8965			1	0.1 0/00
Elderly	**2069**	**25**	**12 0/00**	**2**	**1 0/00**
Male	1035	9	8 0/00		
Female	1034	16	15 0/00	2	2 0/00
Total	**38227**	**154**	**4 0/00**	**16**	**0.4 0/00**

Serious Adverse Events in Phase I - French Club Phase I Register 2004-2009

RELATED AND WORRYING SAE : 16

- Atrial fibrillation – elderly woman (1) + middle-aged overweight man (1)
- Rash and fever – young man (2)
- Anaphylaxis - young woman (1)
- Agranulocytosis – young man (1)
- Cholecystectomy / lithiasis – young man (1)
- Acute liver injuries (increase ALT) – young man (5)
- Convulsions - young man (2) & elderly woman (1)
- Rhabdomyolysis - young man (1)

All subjects recovered

Serious Adverse Events in Phase I - French Club Phase I Register 2004-2009

DEATHS : 4 non drug related

- Cancer (lung): elderly woman
- Motorbike accident: 1 young man
- Suicide: elderly
- Suicide: middle-aged man

Serious Adverse Events in Phase I - French Club Phase I Register 2004-2009

INCIDENCE IN PHASE I

	France	UK
	CPI 2004-2009	AICRC 92-2001
	38227 subjects	92510 subjects
	6371 / year	9000 / year
SAEs incidence per 1000	4	2
Related SAEs incidence per 1000	1.4	1
Worrying and related	16 (0.4$^{0}/_{00}$)	? + 6 (London Te Genero 2006)
Death	4	3
Related deaths	no	no

Low and stable incidence
About 1/3 are drug related

CONCLUSIONS : SAFETY IN PHASE I

During the last 4 decades ,

- 12 deaths were reported worldwide in Phase 1
- 5 were drug related
  - 4 were due to screening default or study misconduct
  - 1 was drug related and unexpected
- 16 worrying drug-related SAEs within last 6 years in France

Phase I is safe even if specific new risks appeared with New Biological Entities (e.g TGN1412)

CONCLUSION : SAFETY IN PHASE I

Phase I is safe.

- **but follow current CPU SOPs and guidelines !**
- **but … pay specific attention to:**
  - **Elderly subjects**
  - **NBEs & high risk compounds**
- **be cautious when conducting FIM studies**
  - **Dose calculation (starting dose, last dose, dose progression)**
  - **number of subjects dosed in the same day,**
  - **dosing interval between subjects and between cohorts**
  - **define stopping rules,**
  - **qualified/ accredited CPUs and investigators and sponsor clinical pharmacologists…**

Thank you for your attention